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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61L 33/00, C08F 20/60 C08B 37/10	AI	(11) International Publication Number: WO 91/16932 (43) International Publication Date: 14 November 1991 (14.11.91)
(21) International Application Number: PCT/GB91/00679 (22) International Filing Date: 29 April 1991 (29.04.91) (30) Priority data: 9009570.4 27 April 1990 (27.04.90) GB (71) Applicant (for all designated States except US): BIOCOMPATIBLES LIMITED [GB/GB]; Brunel Science Park, Kingston Lane, Uxbridge, Middlesex UB8 3PQ (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : BAMFORD, Clement, Henry [GB/GB]; AL-LAMEE, Kadem, Gayad [IQ/GB]; The University of Liverpool, First Floor, Duncan Building, Royal Liverpool Hospital, P.O. Box 147, Liverpool L89 3BX (GB).		(74) Agents: CRESSWELL, Thomas, Anthony et al.; J.A.Kemp & Co, 14 South Square, Gray's Inn, London WC1R 5LX (GB). (81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: ANTITHROMBOGENIC POLYMERS (57) Abstract Polymers bearing heparin residues in bioactive form may be used in blood-contacting devices and as affinity chromatography agents. The polymers are produced by (a) polymerising heparin-bearing vinyl, acrylate, acrylamide or acrylonitrile monomers, (b) free-radical polymerisation of monomers in the presence of heparin or (c) grafting heparin to polymers via amino-group containing side chains.		

Antithrombogenic Polymers

The present invention relates to polymers having reduced thrombogenicity by virtue of stable covalent bonding of heparin. The invention also relates to processes for
5 producing such polymers, monomers for use in the production of the polymers and uses of the polymers.

There is a continuing need for improved means for reducing the thrombogenicity of polymers commonly used in the manufacture of blood-contacting medical apparatus such
10 as blood transfusion and blood-handling equipment and in prostheses and implants. Heparin is known to have blood-clot formation-preventing properties but has previously been used mainly in situations where non-covalent bonding is sufficient in view of difficulties in creating stable
15 covalent bonding whilst retaining the bioactivity of the heparin. Degraded heparin has been covalently bonded to surfaces and used clinically [Larm, O. et al, Biomater. Med. Dev. Artif. Organs, 11, 161 (1983); Larsson, R. et al, Ann. N.Y. Acad. Sci., 516, 102(1987) and Olsson, P., Inter.
20 J. Art. Org., 13, 594(1990)] but undegraded heparin has not, to date, been coupled satisfactorily to surfaces in a clinically useful manner.

The present inventors have devised means for coupling heparin to polymers by stable covalent bonds whilst
25 retaining the bioactivity of the heparin.

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Accordingly the present invention, in one aspect, provides a polymer having heparin residues covalently bound to the polymer chains in bioactive form.

The covalent binding of heparin and its bioactivity can
5 be tested by techniques described in the Example below.

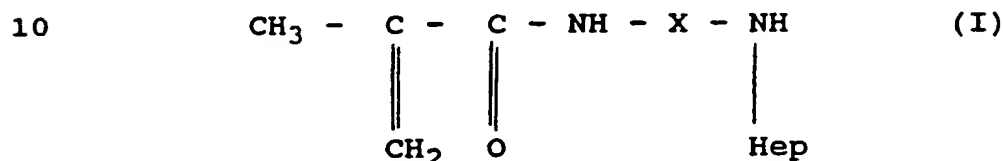
Typical polymers according to the invention are homo- and co-polymers of vinyl monomers, acrylates, alkyl acrylates, alkacrylates and alkyl alkacrylates, acrylonitrile, acrylamide, alkylene glycol acrylic and
10 alkacrylic esters and monomers having reactive double bonds polymerisable by free radical techniques. Hydrogels may be produced by use of water-soluble co-monomers.

Heparin may be coupled to the monomer units before polymerisation to form the antithrombogenic polymers of the
15 invention. Alternatively, polymerisation may be conducted in the presence of heparin such that the heparin molecules become terminally attached to the polymer chains by chain transfer. In a further alternative heparin may be bonded to pre-formed polymers with appropriate reactive side
20 chains. These processes form further aspects of the invention.

In a further aspect of the invention there is therefore provided a process for producing an antithrombogenic polymer which comprises polymerising monomers bearing
25 heparin residues. In principal any monomer polymerisable by a free radical reaction may be used, for instance vinyl

- 3 -

monomers such as N-vinyl pyrrolidone and the acrylate and alkacrylate-type monomers. Monomers bearing heparin residues are hereafter referred to as heparin macromers. Preferred heparin macromers are acrylate or styrene derivatives having heparin bound via amino-group containing substituents and amino-group containing vinyl monomers. The most preferred heparin macromers are those of formula (I).



15 wherein X is a divalent poly(alkylene oxide) chain, preferably containing 10 to 40 alkylene oxide repeating units, or a divalent alkylene group, preferably containing up to 15 carbon atoms, which may be straight, branched or cyclic; and Hep is a heparin residue. Since the

20 poly(alkylene oxide) chain or alkylene group X acts as a spacer between the polymer backbone and heparin molecules, the nature of X influences the bioactivity of the polymer; X will be selected on the basis of routine tests to provide the desired biological properties.

25 Preferred heparin macromers of formula (I) are those wherein X is a straight alkylene, more preferably alkylene

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of formula (IIa)



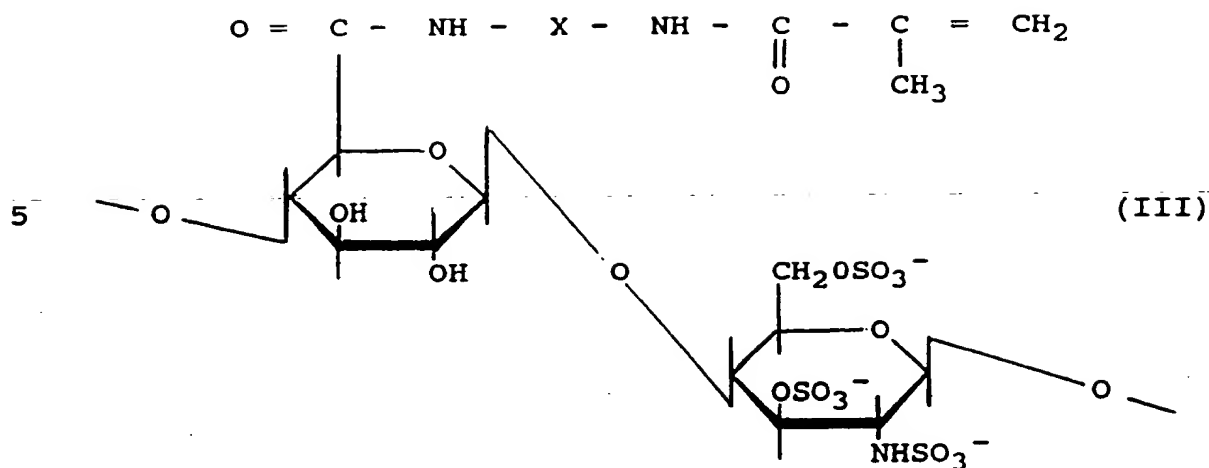
5 wherein n is 3, 6 or 12.

or a poly(alkylene oxide) chain of formula (IIb)



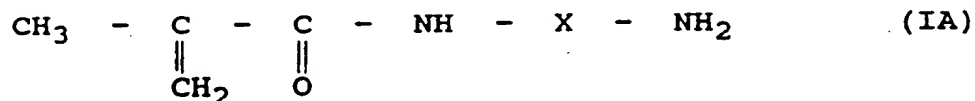
10 wherein m is 10 to 40.

The group Hep is a residue of heparin coupled via an amide or sulphonamide group. Usually the heparin residue will bear a number of covalently coupled monomer units, for
15 instance up to about 40, more preferably from 5 to 30 such as 10, 15, 20 or 25 monomer units per heparin residue. Each monomer unit is coupled via an amide or sulphonamide group of heparin but coupling via carbonyl groups is preferred; this is shown in formula (III) below which shows
20 a portion of a heparin residue bearing a monomer unit:



The macromers of formula (I) above are novel and form a further aspect of the present invention.

The macromers of formula (I) may be produced by reacting a compound of formula (IA)



wherein X is as hereinbefore defined, with heparin in aqueous solution in the presence of a coupling agent.

20 Suitable coupling agents include 1-ethyl-3-(3-dimethyl
aminopropyl) carbodiimide (EDC) and 1-cyclohexyl-3-(2-
morpholinoethyl)carbodiimide metho-p-toluenesulphonate
(CMCI). EDC is preferred. Some purely ionic attachment
of heparin to the compound of formula (IA) may be expected
25 but covalently bonded heparin macromers of formula (I) are
readily separated by solvent extraction, for instance by

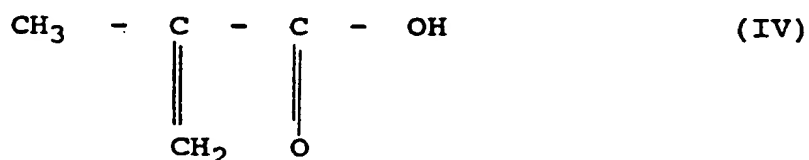
- 6 -

precipitating the product using a lower alcohol such as methanol (in which the compounds of formula (IA) are very soluble) optionally containing hydrogen chloride.

The present invention further provides a process for
 5 producing a heparin macromer of formula (I) as hereinbefore defined comprising reacting heparin with a compound of formula (IA) in aqueous medium and optionally separating the covalently bonded product of formula (I) from non-covalently bound compound of formula (IA) and/or heparin.

10 Preferably the reaction is conducted at room temperature although elevated temperature may be employed provided that the heparin is not degraded thereby. Preferably the reaction is conducted at or near physiological pH and ionic concentration, for instance in a suitably buffered aqueous
 15 medium such as phosphate buffered saline (PBS). Further conventional purification steps may be employed, for instance redissolving the product in aqueous medium and reprecipitation using a lower alcohol such as methanol or methanolic hydrogen chloride.

20 The compound of formula (IA) may be produced by conventional techniques, for instance by reacting the compound of formula (IV) or a reactive derivative thereof



25

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with a diamine of formula (V)



5

wherein X is as hereinbefore defined.

The procedure described in British Patent Application No. 7848702 may be used in which, for instance, a diamine
10 is reacted with methacroyl chloride in the presence of methacrylic acid. In addition to acid halides, other reactive derivatives which may be used include conventional derivatives such as acid anhydrides.

The heparin macromers of formula (I) may be polymerised
15 by conventional free-radical techniques with exclusion of oxygen. Since most macromers contain more than one acrylic carbon-carbon double bond the polymers will generally be cross-linked provided that polymerisation is continued for sufficient duration and to a sufficient degree of monomer
20 conversion.

The heparin macromers are preferably copolymerised with other suitable monomers such as acrylonitrile and acrylamide. It has also been found that the heparin macromers of formula (I), especially those containing more
25 than 25 double bonds per molecule, are soluble in alkylene glycols (such as ethylene glycol) and may thus be

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copolymerised in an alkylene glycol solvent with other vinyl monomers to form polymers containing heparin residues. One such vinyl monomer for copolymerisation with the macromers of formula (I) is ethylene glycol methacrylate, which leads to the formulation of polymers bearing poly(ethylene glycol) chains which have the further advantage of the passivation effect of poly(ethylene glycol) (PEG) and its homologues.

Polymerisation is conducted in a suitable solvent such as formamide, N,N-dimethylformamide or, for water soluble monomer mixtures, aqueous media or, as described above, in alkylene glycols, together with a radical initiator such as azobisisobutyronitrile or, when conducted in aqueous media, a water soluble initiator such as azocyanovaleic acid.

The reaction should be conducted in the absence of oxygen; preferably the reagent mixture is degassed and, if necessary, the polymerisation is conducted under a blanket of inert gas.

The polymerisation reaction may be conducted at room or elevated temperature provided that the temperature is not such as to degrade the polymer or the heparin. A preferred temperature range is from 20 to 100°C, for instance 20 to 80°C, more preferably about 70°C.

The polymer produced may be recovered and purified by conventional techniques such as by precipitation, centrifugation and washing.

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The present invention also provides a process for producing an antithrombogenic polymer comprising polymerising a heparin macromer of formula (I) as hereinbefore defined.

5 In a further aspect of the invention there is provided a process for producing an antithrombogenic polymer which comprises polymerising a monomer in the presence of heparin by a radical polymerisation reaction.

Heparin molecules contain a large number of active
10 hydrogen atoms which may partake in a chain transfer reaction whereby a polymer chain growing by a free radical reaction interacts with a heparin molecule, abstracting hydrogen from the heparin and terminating chain propagation (elongation) but creating a heparin free radical which
15 initiates growth of a new polymer chain. In this way polymer chains terminating in heparin residues are formed. Since the same heparin molecule may participate in a number of chain transfer (hydrogen abstraction) reactions, if the reaction proceeds for long enough polymers having several
20 polymer chains per heparin residue will be formed.

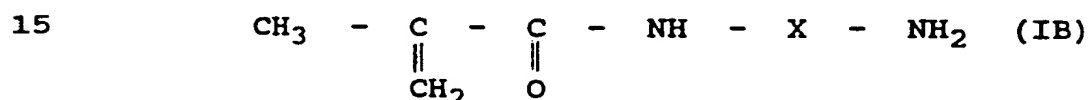
Typical radical polymerisation reactions involve monomers such as acrylates, alkylacrylates, alkacrylates, alkyl alkacrylates, acrylamide and acrylonitrile and vinyl monomers such as vinylacetate. The reactions are conducted
25 in suitable solvents and at temperatures as described above using appropriate radical initiators.

- 10 -

The present invention therefore provides a process comprising polymerising a monomer in the presence of heparin and a free radical initiator to produce an antithrombogenic polymer. The invention also provides
 5 antithrombogenic polymers producible by such a process.

In a further aspect the invention provides a process for producing an antithrombogenic polymer comprising grafting heparin to amino-group containing side chains on the polymer.

10 Suitable polymers having amino-group containing side chains may be produced by conventional techniques. A particularly preferred class of polymers are those containing repeating units of formula (IB).



for instance obtained by polymerisation or copolymerisation of monomers of formula (IA) as hereinbefore defined.

20 As an alternative to polymerising monomers bearing amine-group containing side chains, preformed polymers may be grafted with amine-group containing moieties which are then used to graft heparin to the polymer. The amine-group containing moieties may be introduced for instance by
 25 reacting the preformed polymer bearing suitable reactive groups with a mono-protected diamine; the unprotected

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amine groups graft to the polymer and the protecting groups are then removed exposing amino groups ready for the grafting reaction with heparin.

The reaction between heparin and the polymer may be
5 conducted in the presence of a suitable coupling agent under conditions similar to those described for the reaction of heparin with compounds of formula (IA) above and separation of covalently bound heparin-grafted polymers from non-covalently bound polymers for instance by solvent
10 extraction.

The invention further provides anti-thrombogenic polymers obtainable by grafting heparin residues onto a polymer bearing amino-group containing side chains.

Polymers according to the present invention may be
15 produced in situ as coatings on materials for use as blood-contacting apparatus or they may be produced as films or shaped articles such as tubing and prostheses for use in such a manner. Alternatively the polymers may be used to coat blood-contacting apparatus. Conventional techniques
20 may be employed subject to the need to avoid conditions deleterious to the polymer or to the heparin residues included therein.

The present invention therefore provides a process for coating a blood-contacting surface by in situ
25 polymerisation to form a coating of an antithrombogenic polymer as hereinbefore defined or by applying an

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antithrombogenic polymer as hereinbefore defined on a blood-contacting surface. The invention also provides shaped articles comprising or consisting substantially of an antithrombogenic polymer as hereinbefore defined. The
5 invention further provides the use of an antithrombogenic polymer as hereinbefore defined for reducing the thrombogenicity of a blood-contacting surface.

The polymers of the present invention may also be used as affinity chromatography agents in which immobilised
10 heparin residues on the polymer provide for specific binding to, for instance, antithrombin (III) or growth factors. Preferably the polymers are used in the form of beads or powders. Such beads and powders and separation processes form further aspects of the invention. The
15 polymers of the present invention which comprise the repeating units of water-soluble monomers and are therefore swellable or soluble in water (gels or hydrogels) may be used as therapeutic agents to prevent blood-clotting, for instances by introduction into a body cavity.

20 The invention therefore further provides an anti-thrombogenic polymer as hereinbefore defined for use in a method of treatment of the human or animal body and the use of an antithrombogenic polymer as hereinbefore defined in the production of a medicament for use in the treatment of
25 the human or animal body, for instance as a prosthesis, implant or blood-clot preventing formulation.

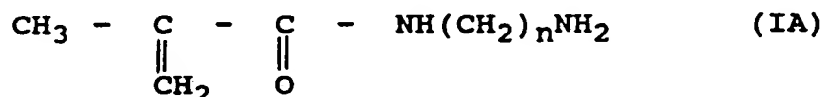
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The invention will now be illustrated by the following Examples which are not intended to limit the scope of the invention in any way:

EXAMPLES 1 TO 3; FORMATION OF HEPARIN MACROMERS

5 Carboxyl groups in heparin are reacted with amino-derivatives of polymerizable vinyl monomers to form polymerizable heparin macromers. Heparin moieties are thus coupled through stable amide links. Coupling was effected in aqueous solution with 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide (EDC) as the coupling agent.

Initially the monomer (IA)



15

n=3, was synthesised by reacting hexamethylene diamine with methacryloyl chloride in the presence of methacrylic acid according to the procedure in UK patent GB 7848702, 16 July 1980. Subsequently this material has obtained from Kodak.

20 The other monomers ((IA), n=6, n=12) were prepared as described above.

Heparin was a commercial product (Fluka), Mwt = 20,000. Heparin labelled with ³⁵S to facilitate analysis of polymer adducts was obtained from Amersham International.

25

Coupling Reaction

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A variety of conditions was used, the aim being to eliminate the possibility of (relatively unstable) ionic binding. For this reason phosphate-buffer saline (PBS) was used in some experiments in place of water as the reaction medium, and precipitation of the product was carried out in methanol containing N/10 hydrogen chloride. (The free amino monomers are very soluble in methanol). Typical reactions are as follows:

Example 1

10 Heparin (0.6g) labelled with ^{35}S was dissolved in water (2ml) and amino-monomer (IA, n=6, 0.13g) in water (1ml) was added together with EDC (0.2g). The mixture was allowed to stand for 24h at room temperatures; the product was then precipitated into
15 methanolic hydrogen chloride, redissolved in water and reprecipitated.

Example 2

Example 1 was repeated using heparin (0.6g), amino
20 monomer (IA, n=6, 0.2g), EDC (0.2g) in water (1ml), PBS (3ml), 24h at room temperatures. The product was precipitated three times into methanolic hydrogen chloride.

25 Example 3

Example 1 was repeated using heparin (0.7g), amino

- 15 -

monomer (IA, $n=3$, 0.23g), EDC (0.4g), PBS (3ml), 36h at room temperatures. The product was precipitated into methanolic hydrogen chloride three times.

5 In these experiments no attempts were made to separate unreacted heparin from the macromer. Indeed, such separation seems unnecessary in practice, since during subsequent polymerisation of the macromer heparin would be relatively unaffected. The products of Examples 1 to 3 are
10 completely soluble in ethylene glycol, whereas heparin is quite insoluble. It would seem, therefore, that little free heparin is present.

From the results of elemental analysis the numbers of double bonds per molecule of the macromers of Examples 1 to
15 3 were found to be:

Example	double bonds
1	14.4
2	23.4
3	36.3

20

taking the M.Wt of heparin as 20,000. The number of -COOH groups in a molecule of heparin is probably about 28, so that unless the value for the macromer of Example 3 is an overestimate, some monomer units may be coupled as
25 sulphonamide derivatives.

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EXAMPLES 4 TO 7; POLYMERISATION OF MACROMERS OF EXAMPLES 1
TO 3

Examples 4 to 6

Soluble copolymers were prepared with acrylonitrile
5 copolymer using formamide as solvent and
azobisisobutyronitrile as initiator at 60°C in the
absence of oxygen. After an appropriate time the
copolymer was precipitated several times into water,
PBS or aqueous hydrogen chloride to remove unreacted
10 macromer. The final material, prepared by
precipitation into water, was a fine powder.

In these Examples the copolymers produced from the
macromer of Examples 1 and 2 had a monomodal
molecular distribution (Examples 4 and 5), that from
15 Example 3 had a bimodal distribution
(Example 6).

Example 7

Gels (hydrogels) are readily prepared by
copolymerisation of the macromers with water-soluble
20 monomers, eg, acrylamide, using a water-soluble
initiator such as azocyanovaleic acid.

EXAMPLE 8; POLY(ETHYLENE GLYCOL) COPOLYMERS

As noted above, heparin macromers are soluble in
ethylene glycol. This property has been exploited in
25 preparing copolymers carrying poly(ethylene glycol) as well
as heparin units.

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The following illustrates the synthesis of a copolymer of a heparin macromer, poly(ethylene glycol) methacrylate (PEGMA) and methyl methacrylate. The heparin macromer of Example 2 (0.05g), PEGMA (0.15g), methyl methacrylate (0.3g) and azobisisobutyronitrile (0.0118g) were dissolved in ethylene glycol (4g) and dimethylformamide (DMF, 4g). The mixture was degassed and polymerised (70°C) for 2h. The reaction product was then poured into ether (50 ml) and methanol was added dropwise until the ethylene glycol had dissolved. The precipitated copolymer was separated by centrifugation and purified by multiple washings and centrifugations. It was insoluble in many common solvents, but dissolved in a methanol-water (1:1 v/v) mixture.

The PEGMA used in the above was prepared by reaction of monomethyl PEG ($\text{CH}_3\text{O}(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$) with methacryloyl chloride in methylene chloride solution in the presence of triethylamine.

EXAMPLE 9; GRAFTING HEPARIN TO A PRE-FORMED POLYMER

20

A copolymer (A) of methyl methacrylate and amino-monomer (IA, $n=12$) was prepared in a solvent consisting of methanol and DMF (5:3 v/v).

Films were cast from the liquid into glass tubes. In a typical case the film was left for 24h in contact with a solution of heparin (^{35}S , 35.4mg) in water (5ml) containing

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CMCI (14.4mg) as coupling agent. The film was washed copiously with water (10 times) and submitted to Soxhlet extraction with water for 3 days.

5 EXAMPLE 10; HEPARIN - CONTAINING POLYMERS BY CHAIN TRANSFER

Experiments were carried out with heparin as transfer agent in the polymerisation of acrylonitrile. In one experiment ^{35}S -heparin (0.1g) in formamide (3ml) was mixed with acrylonitrile (2ml). Polymerisation was carried out
10 (60°C) with azo-bisisobutyronitrile (40 mg) as initiator. The mixture was then poured into water and the precipitated polymer purified by three reprecipitations into aqueous hydrogen chloride. Monomer conversion in this experiment was 5.5%. The product contained 0.82% heparin by weight,
15 according to measurements of radioactivity.

From the heparin content a value at 60°C of the transfer constant of heparin towards acrylonitrile (ie k_f/k_p where k_f is the rate coefficient of chain transfer and k_p is the velocity coefficient for chain propagation) of 0.16 may be
20 calculated. This is a reasonable value for a molecule of MWt. 20,000, containing many potentially reactive hydrogens.

EXAMPLE 11; BIOACTIVITY MEASUREMENTS

25

The bioactivity of the materials of the preceding

- 19 -

Examples was assessed by measurement of conventional partial thromboplastin times (PTT) in human plasma; they are given in Table 1.

- 20 -

Table 1. Partial Thromboplastin Times

Compound or Copolymer	% heparin in copolymer	Heparin concentration ($\mu\text{g/ml}$)	PTT (sec)
Control	N/A	0	124,125,117
Heparin	N/A	0.425	471,494,480
Macromer of Ex 1	N/A	0.427	358,411,396
Macromer of Ex 2	N/A	0.460	388,385,396
Macromer of Ex 3	N/A	0.575	360,351,355
Control	0	0	145,150,147
Ex 4 (powder form)	5.94	83.2	890,876,885
Ex 5 (powder form)	2.00	50.0	725,730,718
Ex 6 (powder form)	11.7	93.6	>1800
Ex 10 (powder form)	0.82	22.4	420,425,421

Evidently the three macromers of Examples 1 to 3 are almost as bioactive as heparin, in spite of the observation that a considerable fraction of carboxyl groups have been substituted (contrast C.D. Ebert, E.S. Lee, J. Deneris and S.W. Kim, Amer. Chem. Soc. Symp. Ser., 199:161(1982); C.D. Ebert and S. W. Kim, Thrombosis Research, 26:43(1982)).

Films cast from solutions of the copolymers of Example 4 to 6 are less active than the powder. A typical PTT experiment gave a clotting time of 510 sec compared to the

- 21 -

control time of 180 sec. In this experiment the film was cast on to a glass tube and it is possible that the heparin molecules tended to associate with the glass surface so that some would be inaccessible. Further, the powders show
5 a much higher specific surface and having been prepared by precipitation into water, the heparin would be expected to be near the surface. One film was incubated with plasma for 24h at 0°C and after this time the plasma was tested; the PTT was the same as that of the control. This shows
10 that there was no leakage of covalently bound heparin into the plasma.

After formation of a clot in one test the clot was removed and the film washed and tested again with fresh plasma. The same result was obtained, indicating no loss
15 in activity arising from elution of heparin.

In the PTT test, 6.6mgs of the copolymer of Example 8 in 1ml plasma gave a clotting time $\gg 2000$ sec, compared to the control figure of 200 sec. The material is therefore very bioactive. A film cast on poly(methyl methacrylate) showed
20 considerable platelet adhesion, although less than pure PMMA.

The polymer film of Example 9 was left in contact with plasma for 48h at 0°C. After further washing with plasma and water a PTT > 540 sec. was found, compared to a control
25 of 34 sec. The final content of heparin in the film was approximately $35\mu\text{g}/\text{cm}^2$.

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Claims

1. A polymer having heparin residues covalently bound in bioactive form to the polymer chains.

5

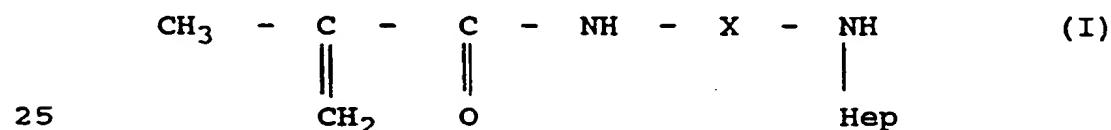
2. A homo- or copolymer according to claim 1 of at least one monomer selected from the vinyl monomers, the acrylate, alkacrylate, alkyl acrylate, alkyl alkacrylate, alkylene glycol acrylate and alkylene glycol alkacrylate
10 monomers, acrylonitrile and acrylamide.

3. A process for producing a polymer according to claim 1 or claim 2 which process comprises polymerising monomers bearing heparin residues.

15

4. A process for producing a polymer according to claim 1 or claim 2 which process comprises free-radical polymerisation in the absence of oxygen of a heparin macromer of formula (I)

20



25

wherein X is a divalent alkylene group or a poly(alkylene oxide) chain

5-



and Hep is a heparin residue.

15

20



with heparin in aqueous solution in the presence of coupling agent.

30

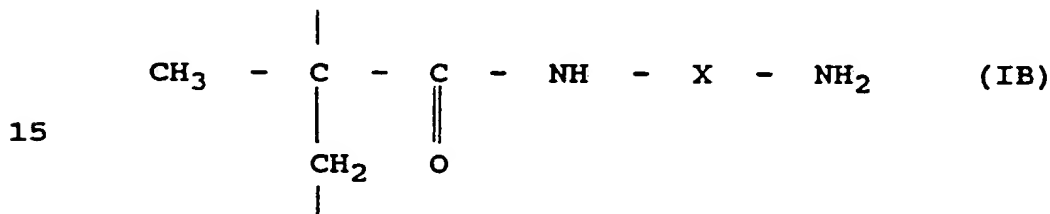
7. A process for producing a polymer according to claim 1 or claim 2 which process comprises free-radical

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polymerisation of a free-radical polymerisable monomer in the presence of heparin.

8. A process for producing a polymer according to claim 1 or claim 2 which process comprises grafting heparin to amine-group containing side chains on the polymer.

9. A process according to claim 8 comprising grafting heparin to a polymer comprising repeating units of formula (IB)



20 wherein X is a divalent alkylene group or a poly(alkylene oxide) chain.

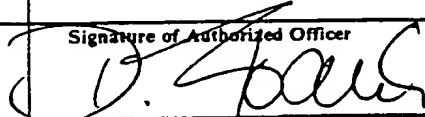
10. A film or shaped article having a blood-contacting surface coated with a polymer according to claim 1 or claim 2 or formed of a polymer according to claim 1 or claim 2.

11. A polymer according to claim 1 or claim 2 for use in a method of treatment of the human or animal body or in a method of diagnosis practised on the human or animal body.

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12. Use of a polymer according to claim 1 or claim 2 in
the production of a medicament or device for use in a
method of treatment of the human or animal body or in a
5 method of diagnosis practised on the human or animal body.

13. An affinity chromatography agent comprising heparin
residue in bioactive form covalently bound to a polymer
support.

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl.5 A 61 L 33/00 C 08 F 20/60 C 08 B 37/10		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl.5	A 61 L C 08 F C 08 B	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	DE,A,3109141 (FRAUNHOFER) 23 September 1982, see page 10, claims 1,2,4 ---	1,2,8, 10
X	WO,A,8700060 (BATTELLE) 15 January 1987, see claims 1,2 ---	1,2,10
A	---	8,9
X	EP,A,0351314 (TERUMO) 17 January 1990, see page 5, line 13; claims 1-4 ---	1,2,8, 10
X	EP,A,0294905 (SETRON) 14 December 1988, see claims 1,6,11,12,13,32; figure 1 ---	1,8,10
X	US,A,4521564 (D.D. SOLOMON et al.) 4 June 1985, see claims 1,2,22,23 --- -/-	1,8,10
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
31-07-1991	24.09.91	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE		
	Mme Dagmar FRANK	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
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X	EP,A,0046828 (TEIJIN) 10 March 1982, see claims 1,7 ---	1,10
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**ANNEX TO THE INTERNATIONAL SEARCH REPORT
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